

ATP Citrate Lyase (ACL) catalyzes the production of cytosolic acetyl CoA

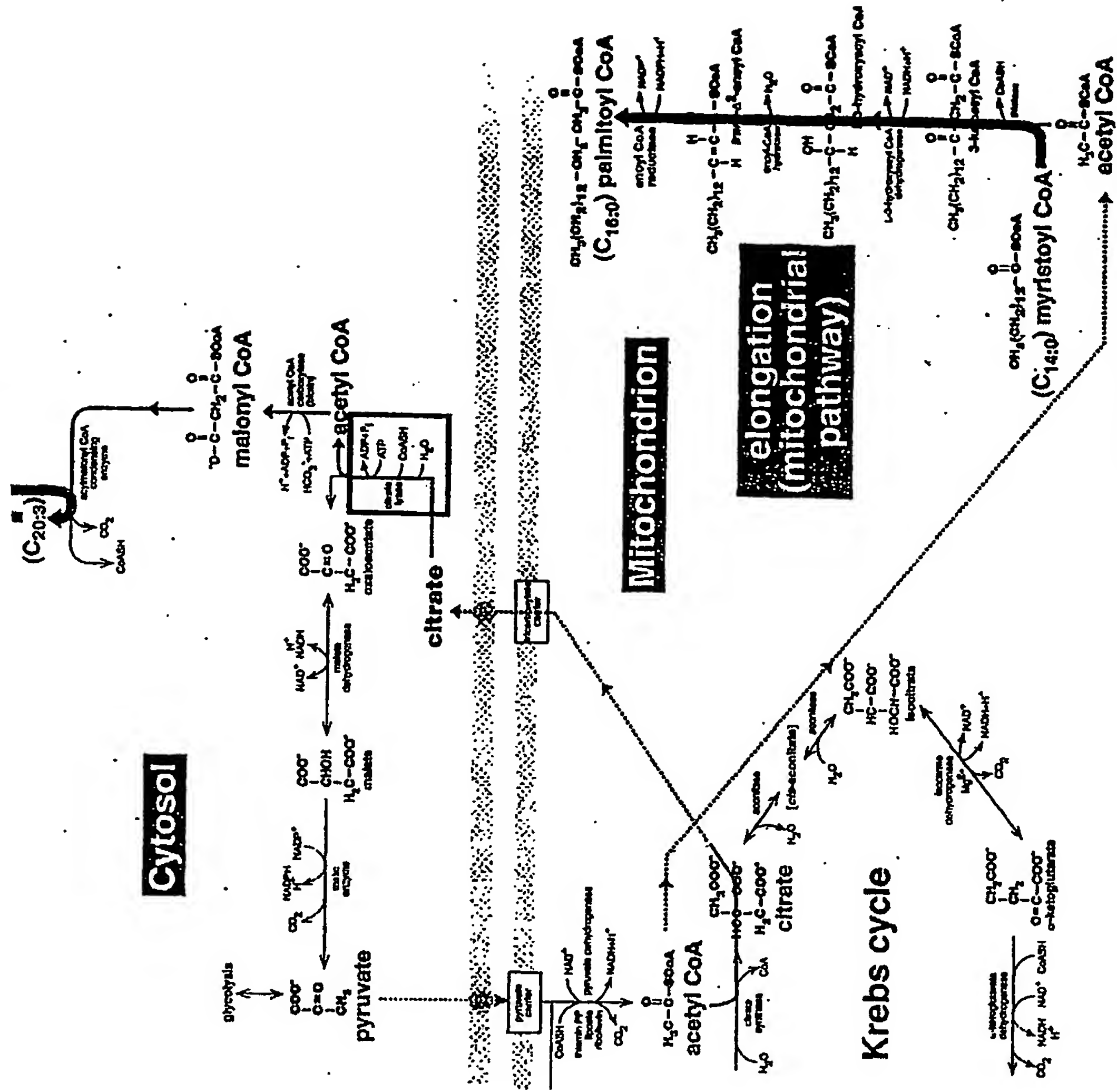


Figure 1

Adapted from: "Metabolism at a glance" (1999)
J.G.Salway (Blackwell Science Ltd, England)

ACL activity is downregulated in quiescent cells via
a post-transcriptional mechanism

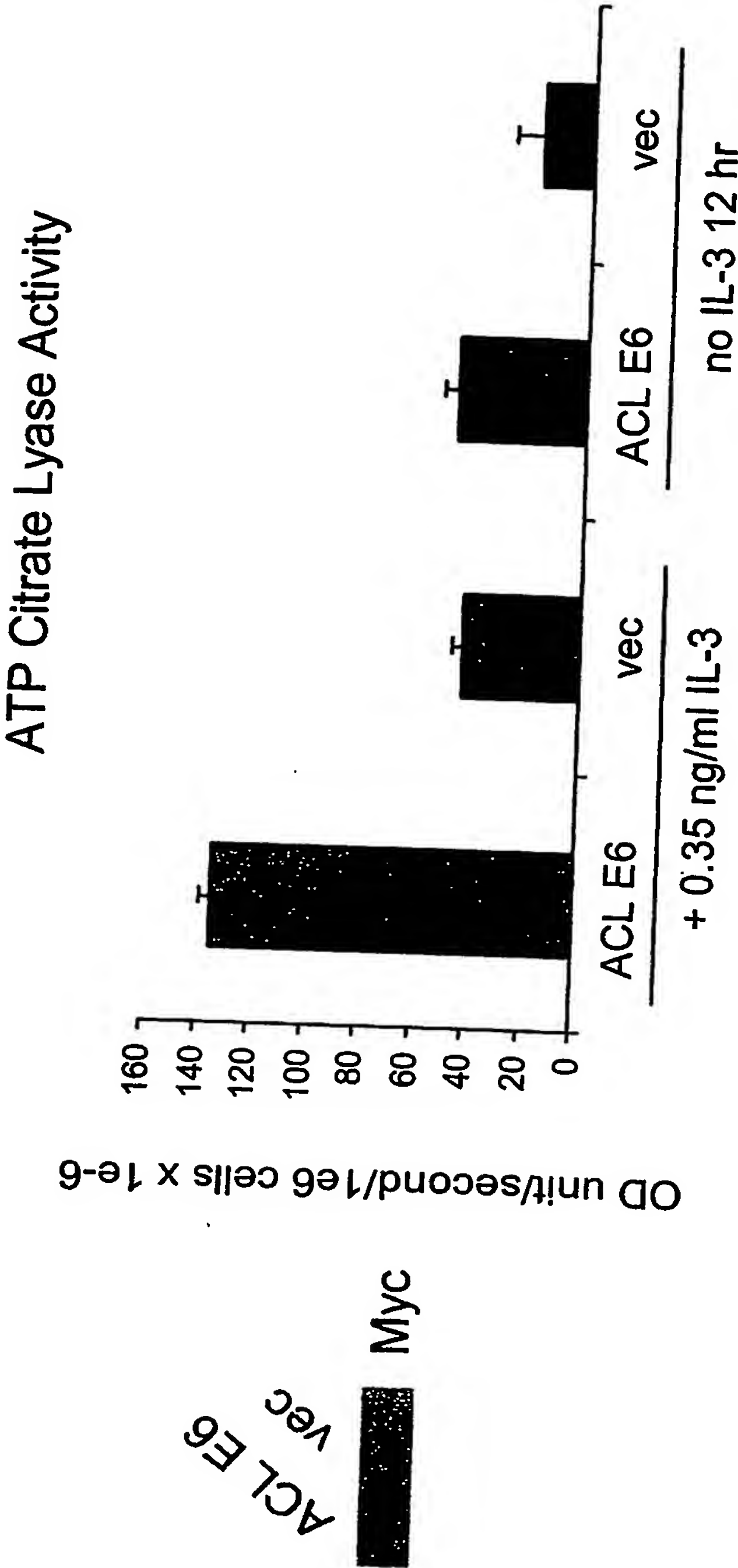


Figure 2

(-)-Hydroxycitrate inhibits cell survival in a dose-dependent fashion at millimolar concentrations

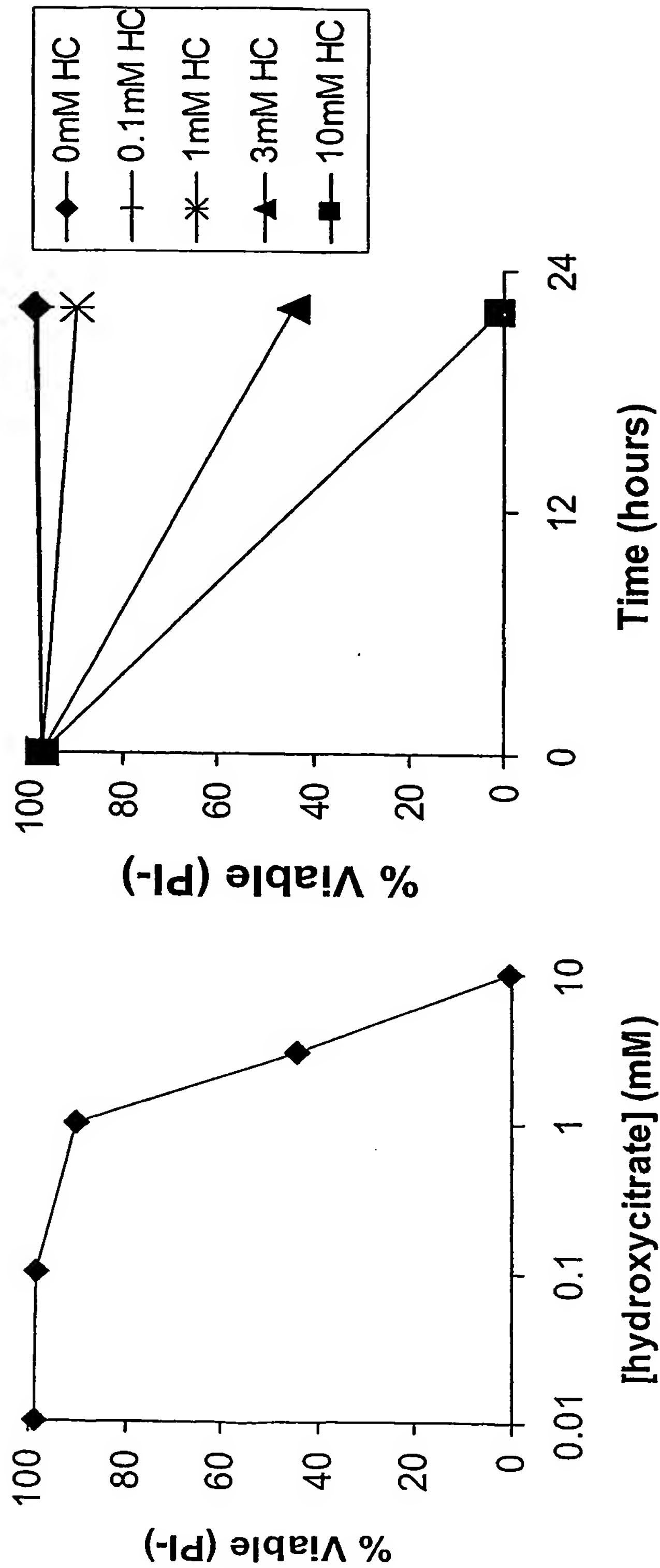


Figure 3

Structure of a potent ACL inhibitor and its prodrug

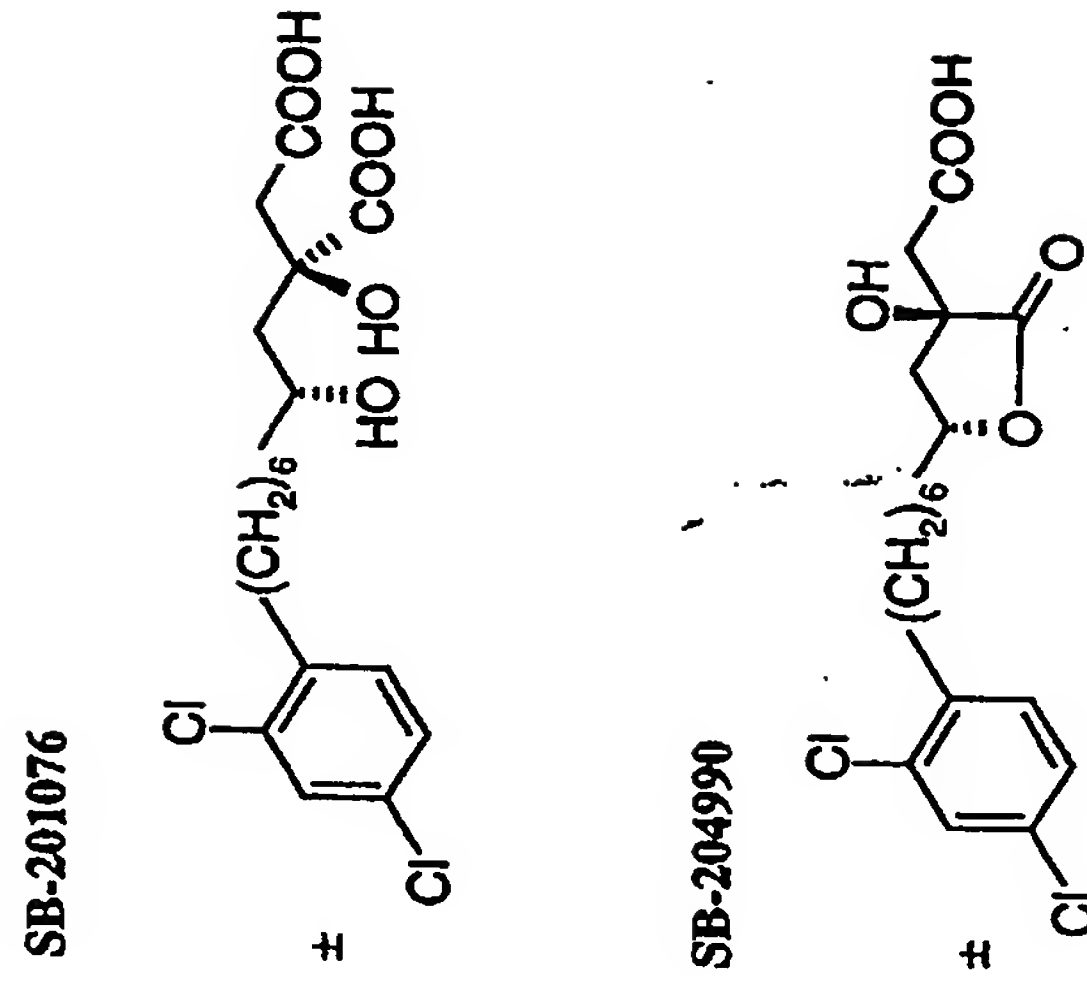


Figure 1 Structure of SB-201076 and its γ -lactone SB-204990

Figure 4

Pierce N.J., et al. (1998) The role of ATP citrate-lyase in the metabolic regulation of plasma lipids. Biochem J. 334, p113-119

SB201076 inhibits ACL activity in a dose-dependent fashion

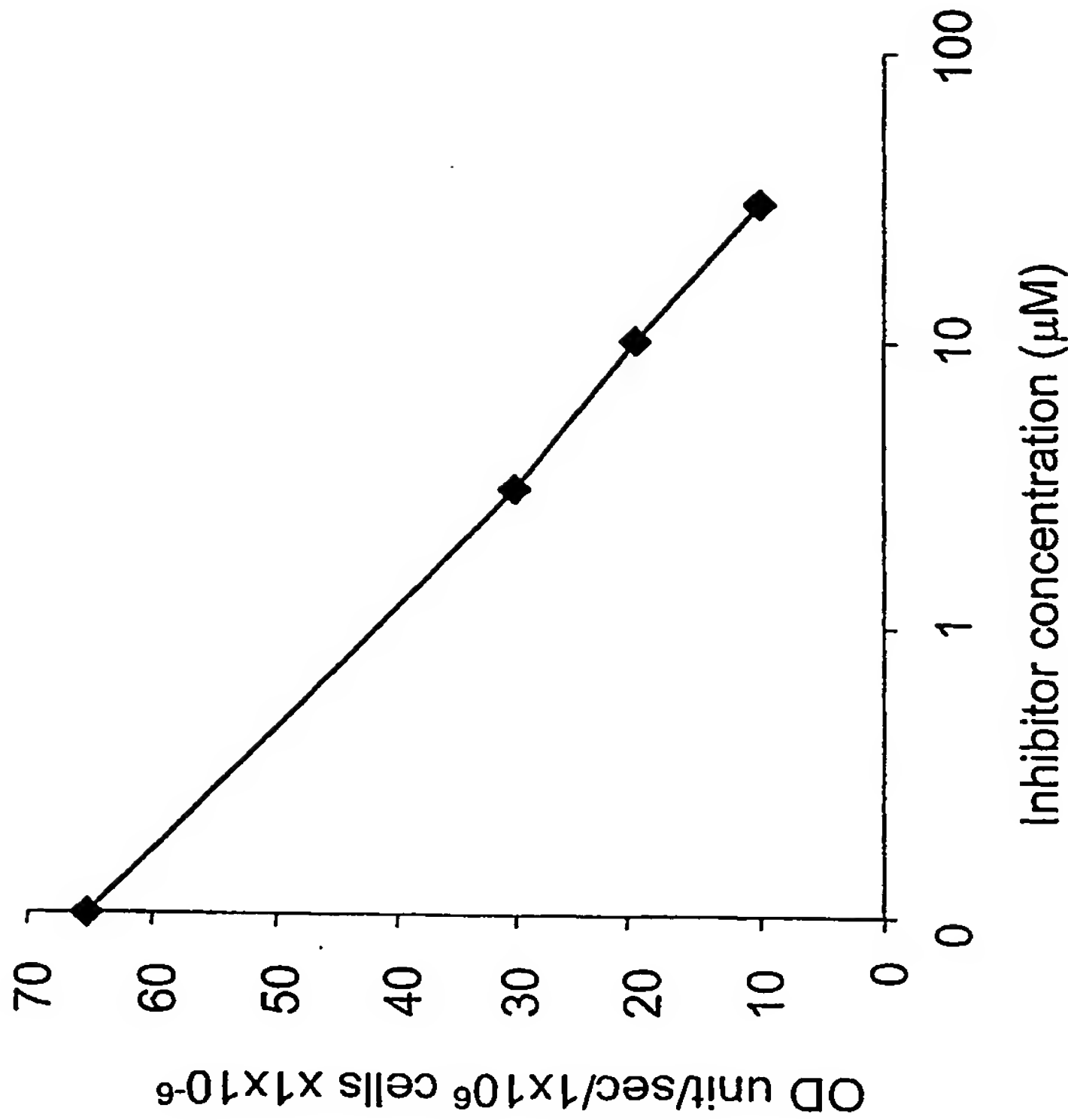


Figure 5

**SB204990 inhibits cell proliferation and survival
in a dose-dependent fashion at micromolar concentrations**

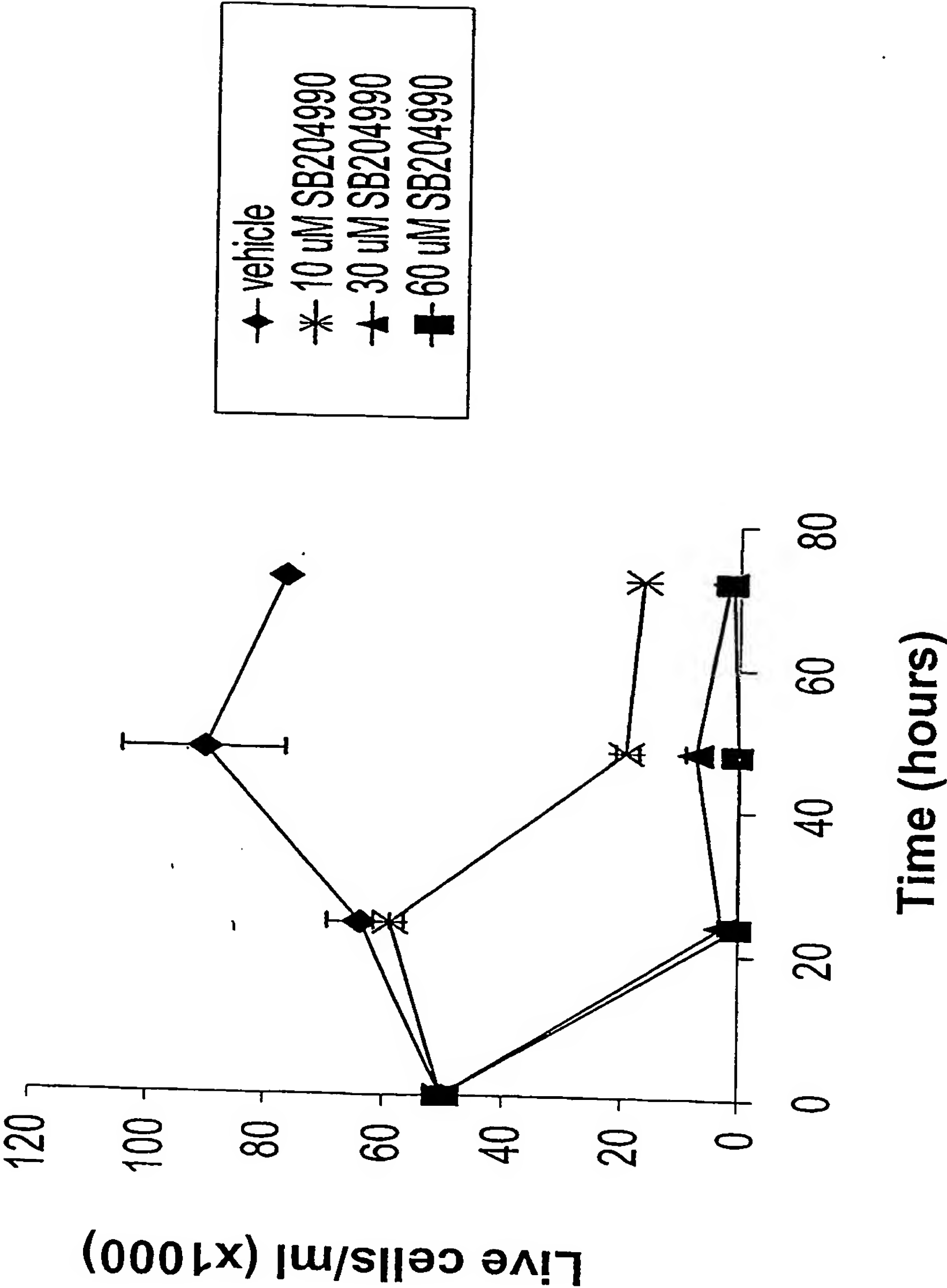
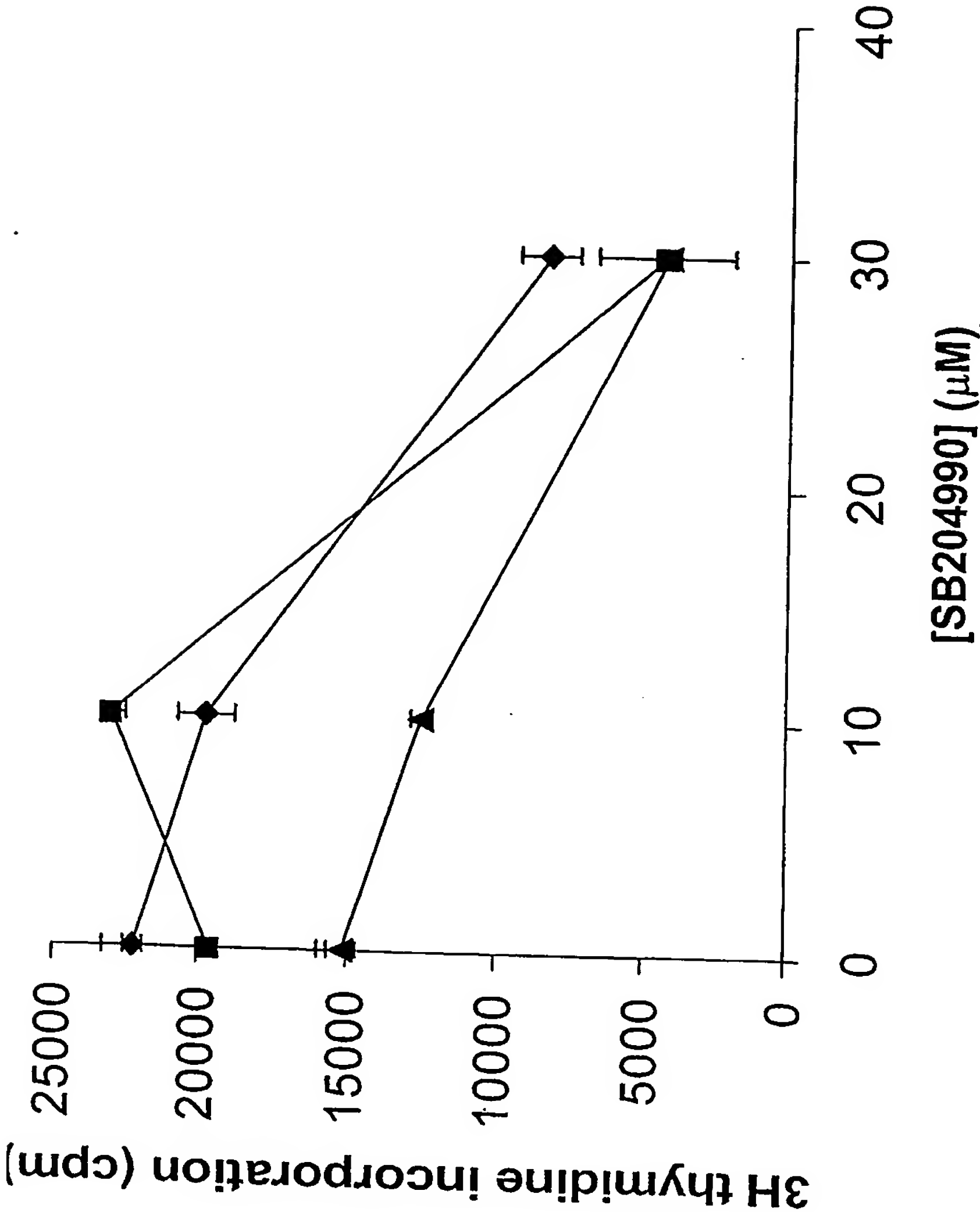


Figure 6

ACL inhibition prevents the proliferation of immortalized hematopoietic cells in a dose-dependent fashion



(3 independent FL5.12 stable clones treated with the drug in the presence of IL3 for 20 hrs)

Figure 7

ACL inhibition causes G1 arrest and apoptosis
of proliferating cells

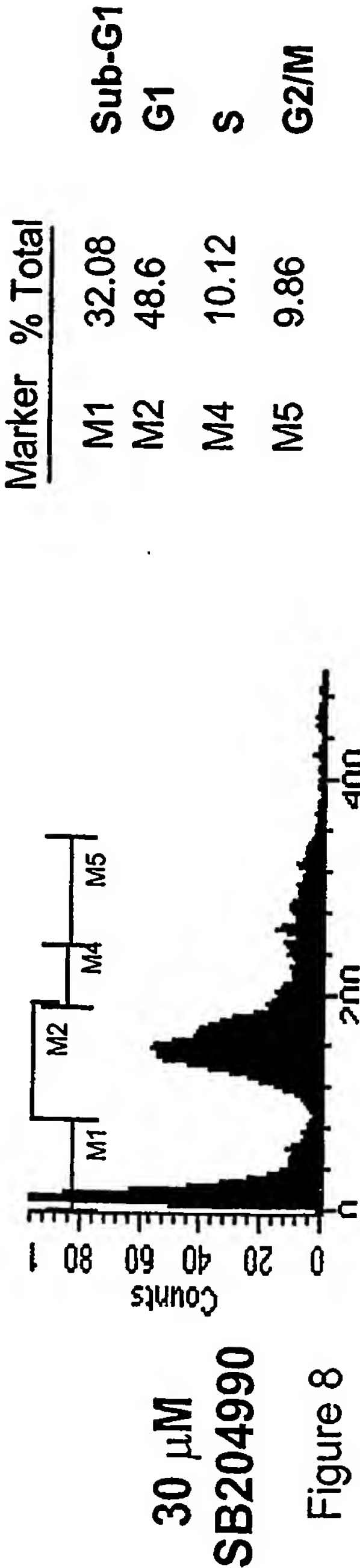
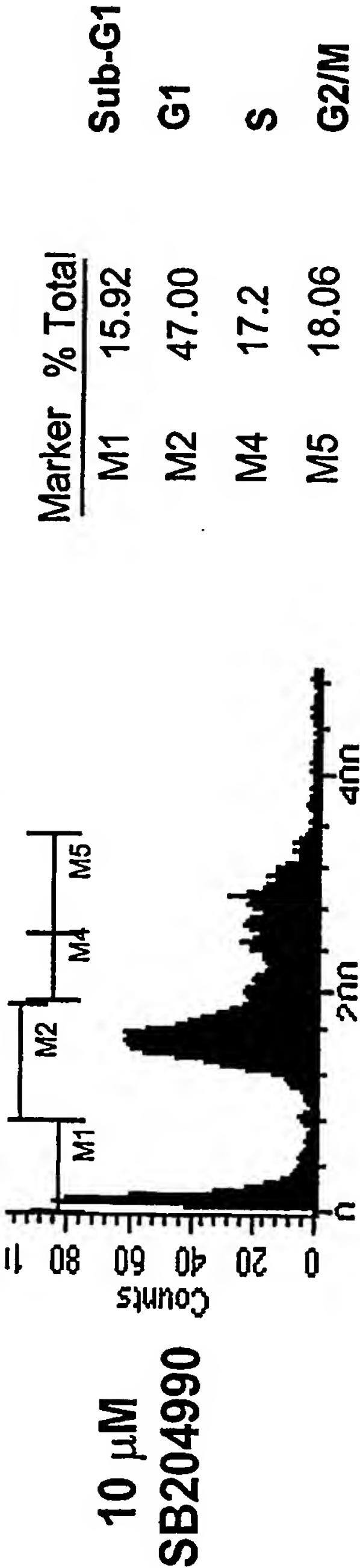
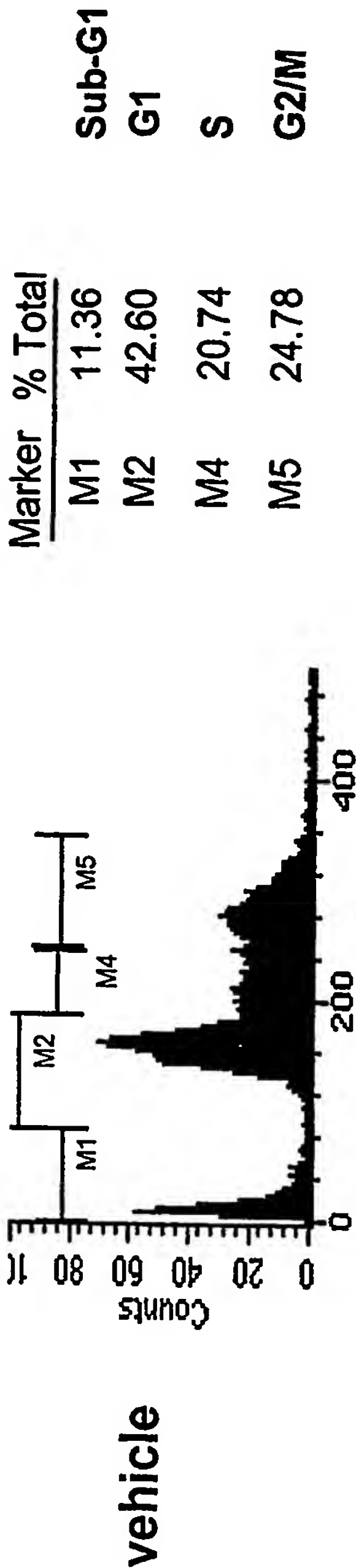


Figure 8

ACL inhibition induces the surface expression of the apoptotic marker Annexin V in a dose-dependent fashion

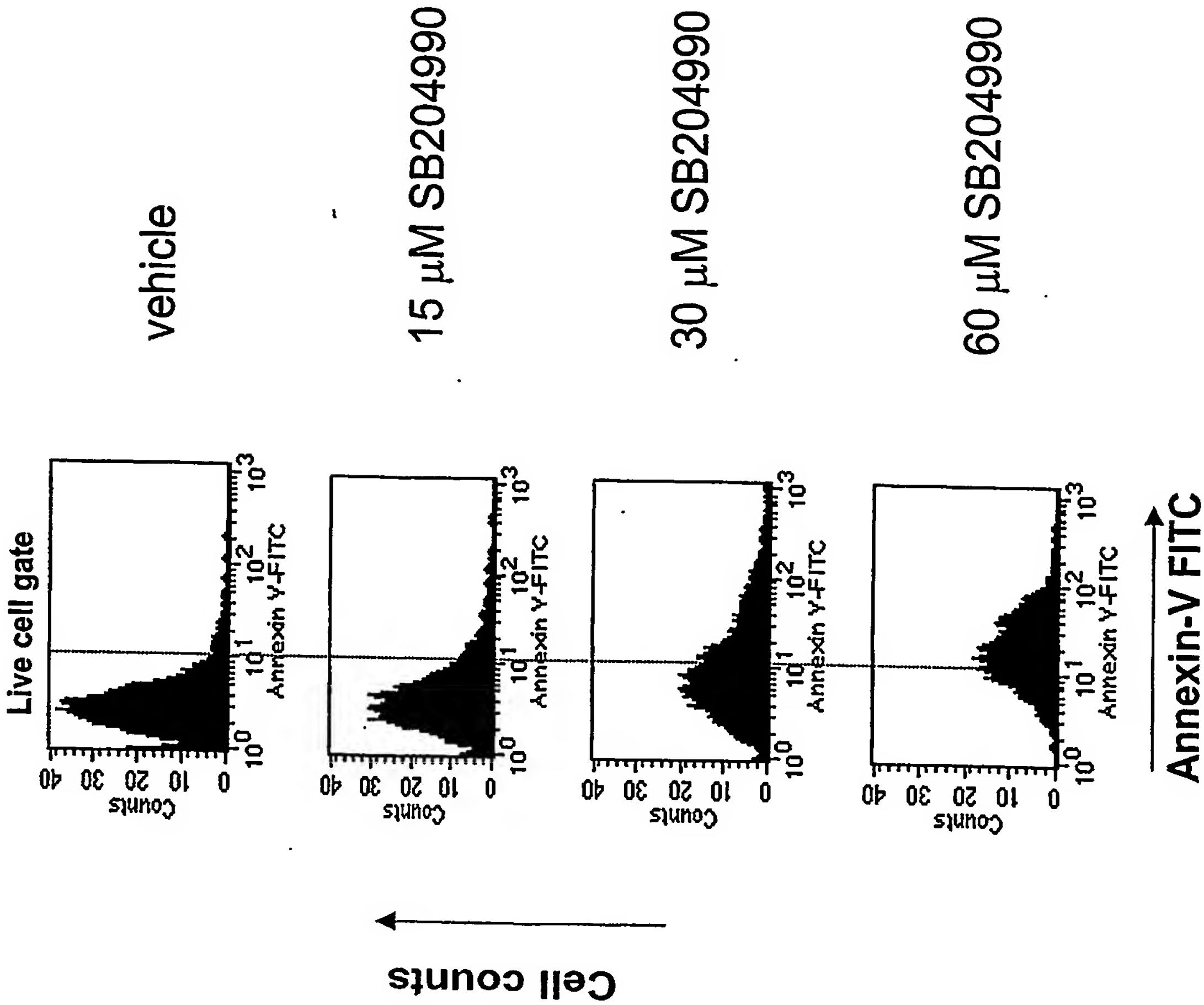


Figure 9

**Akt induces ACL activity independently
of growth factor availability**

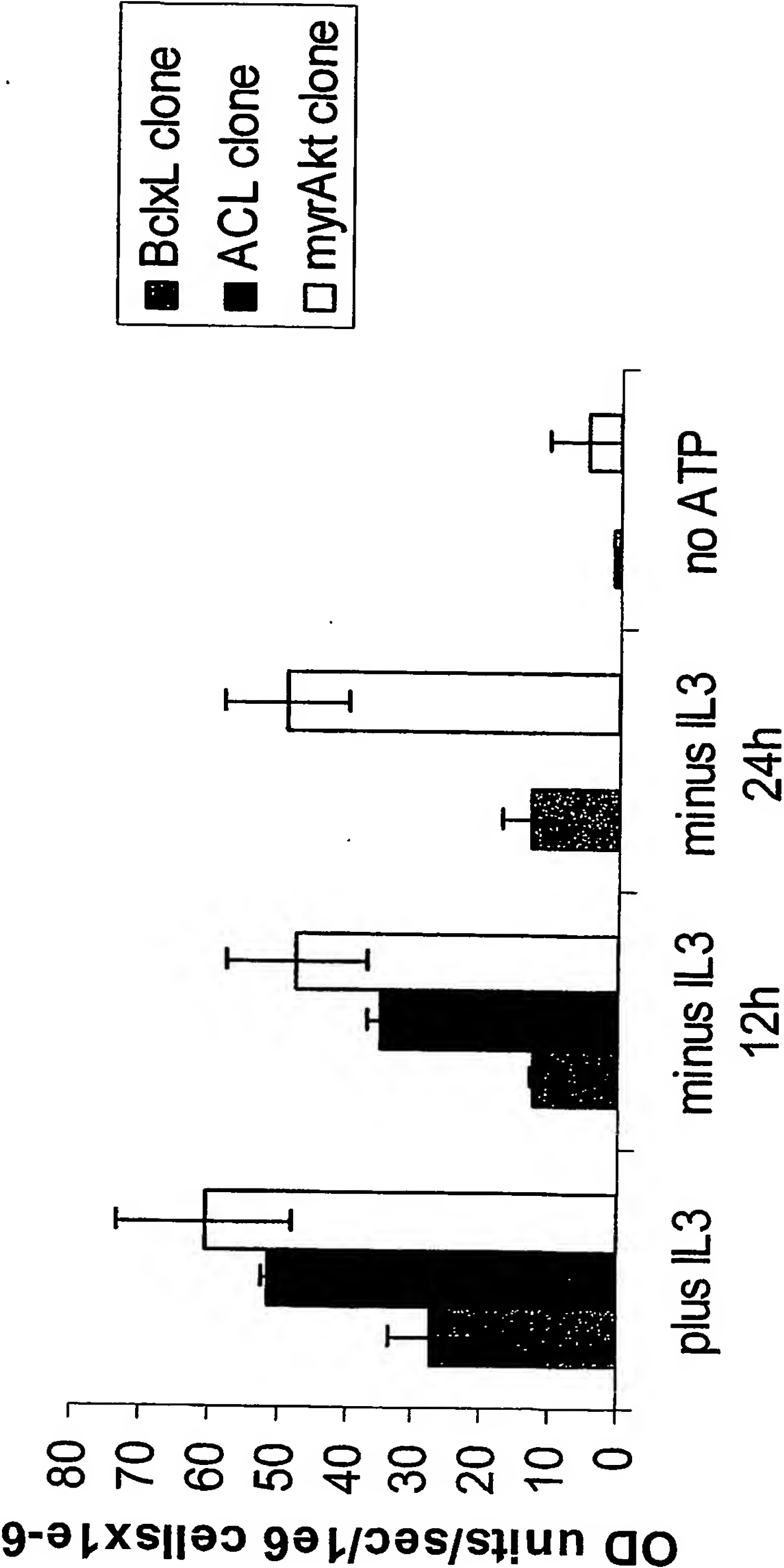


Figure 10

ACL inhibition is selectively toxic to proliferating cells
and to cells expressing active Akt

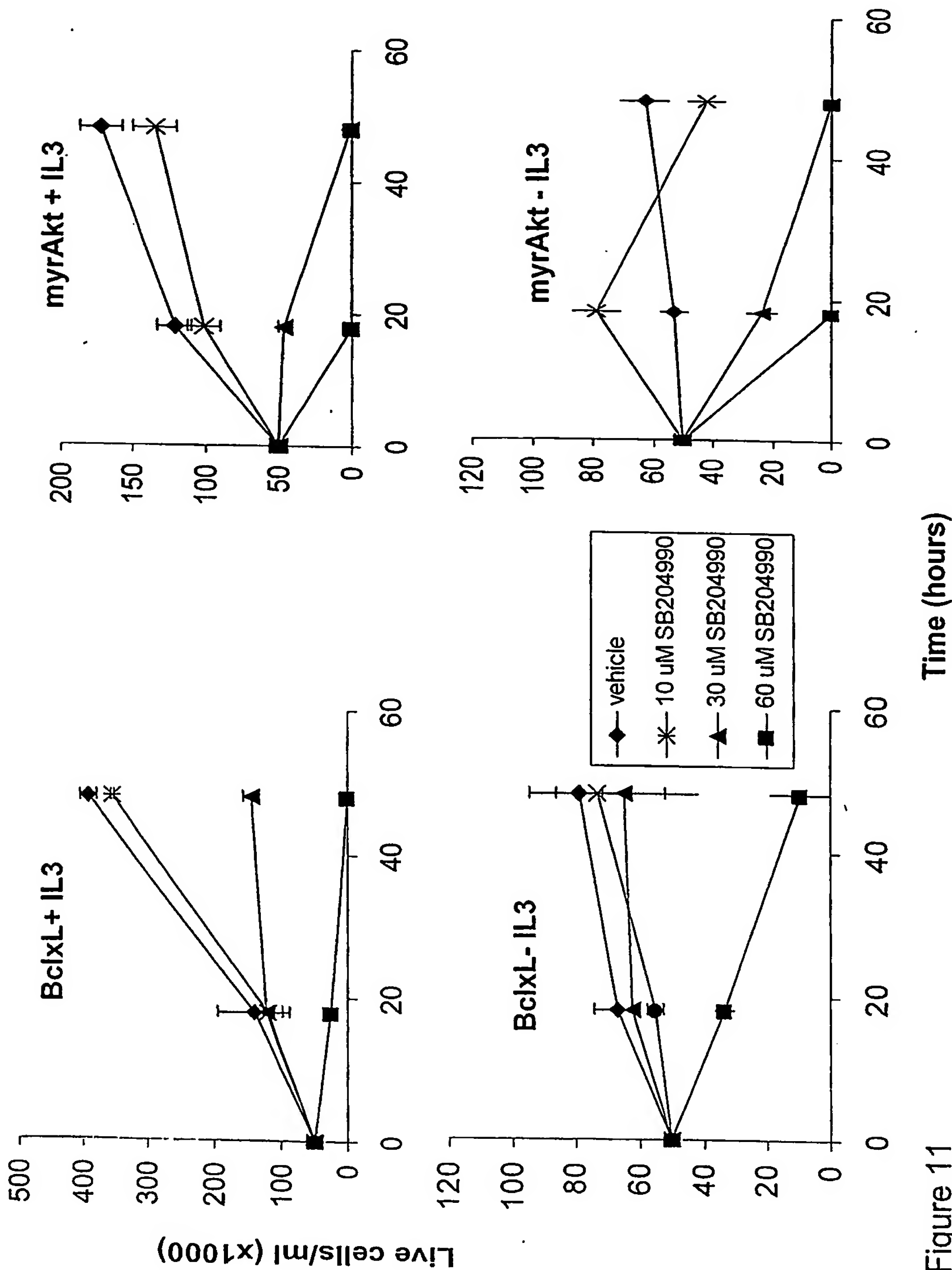


Figure 11

Glioblastoma cell lines' response to ACL inhibition correlates with their activated Akt status

A

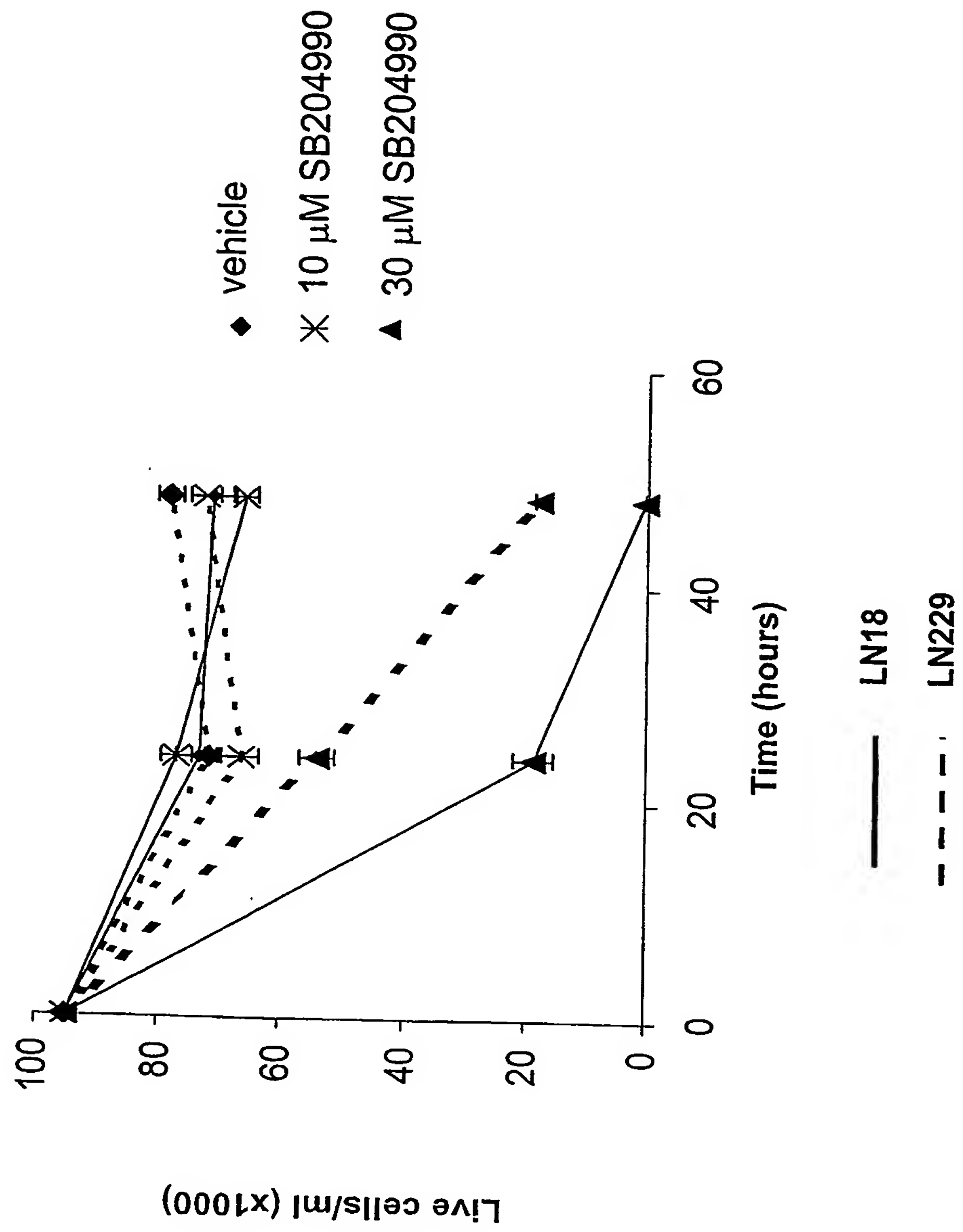


Figure 12A

Glioblastoma cell lines' response to ACL inhibition
correlates with their activated Akt status

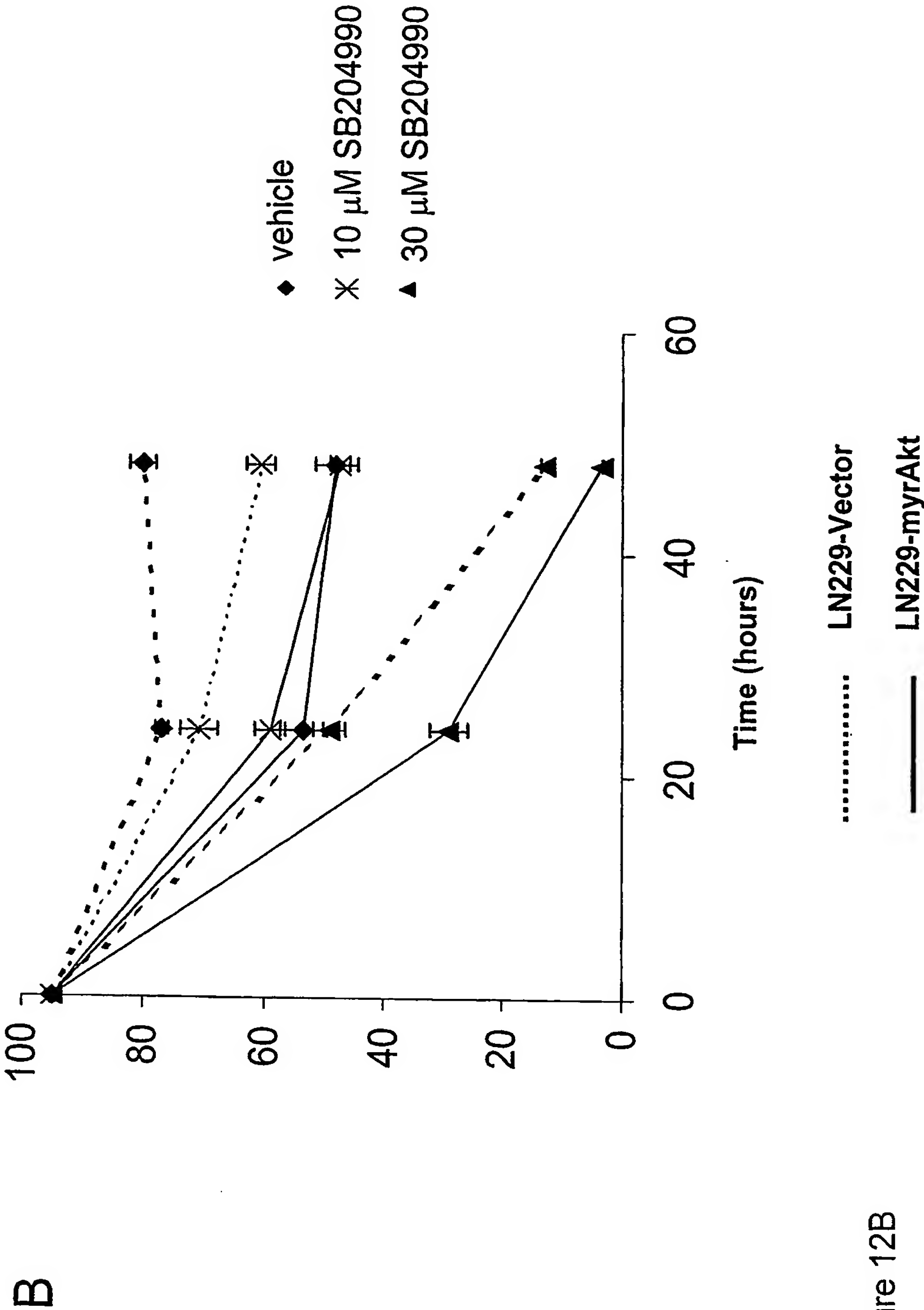
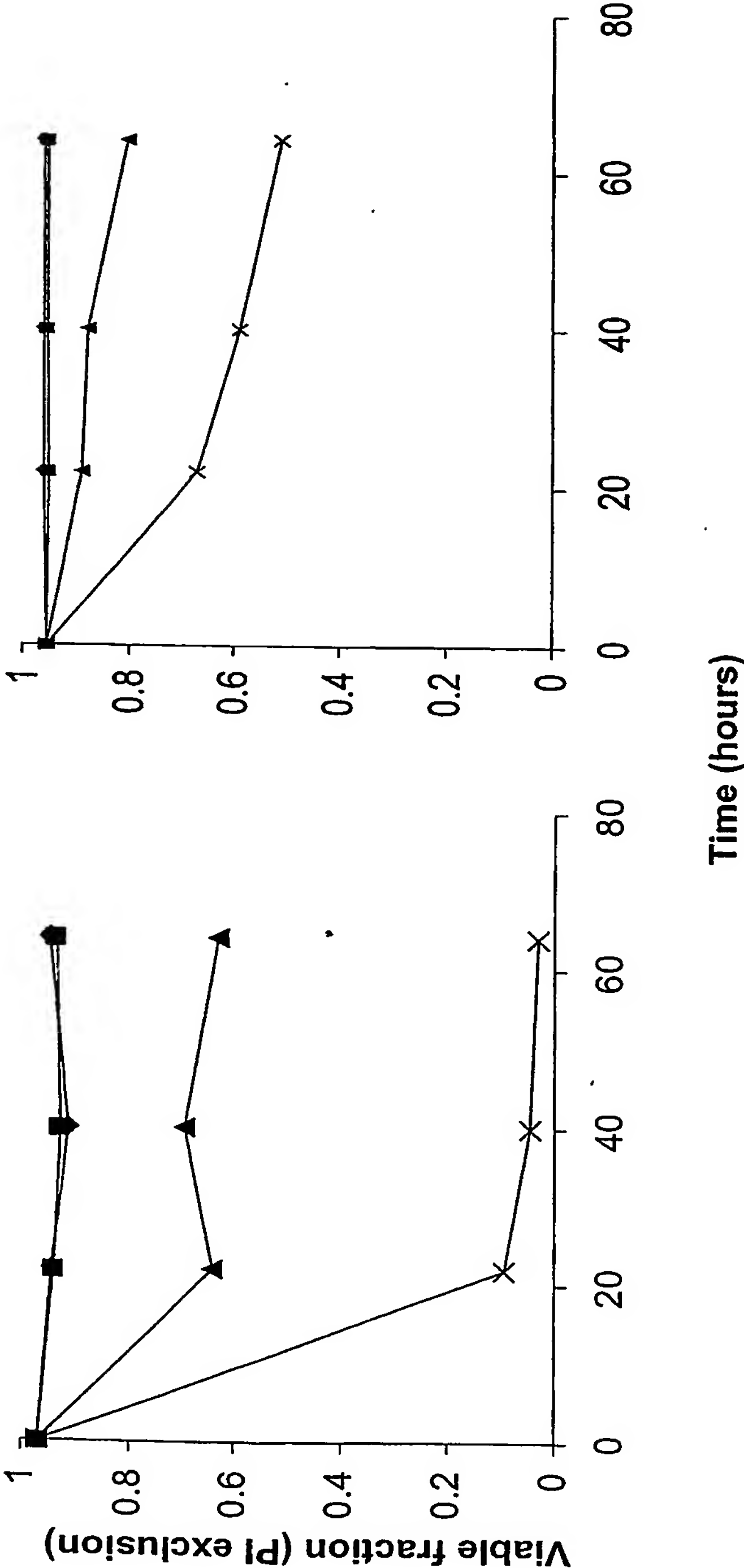


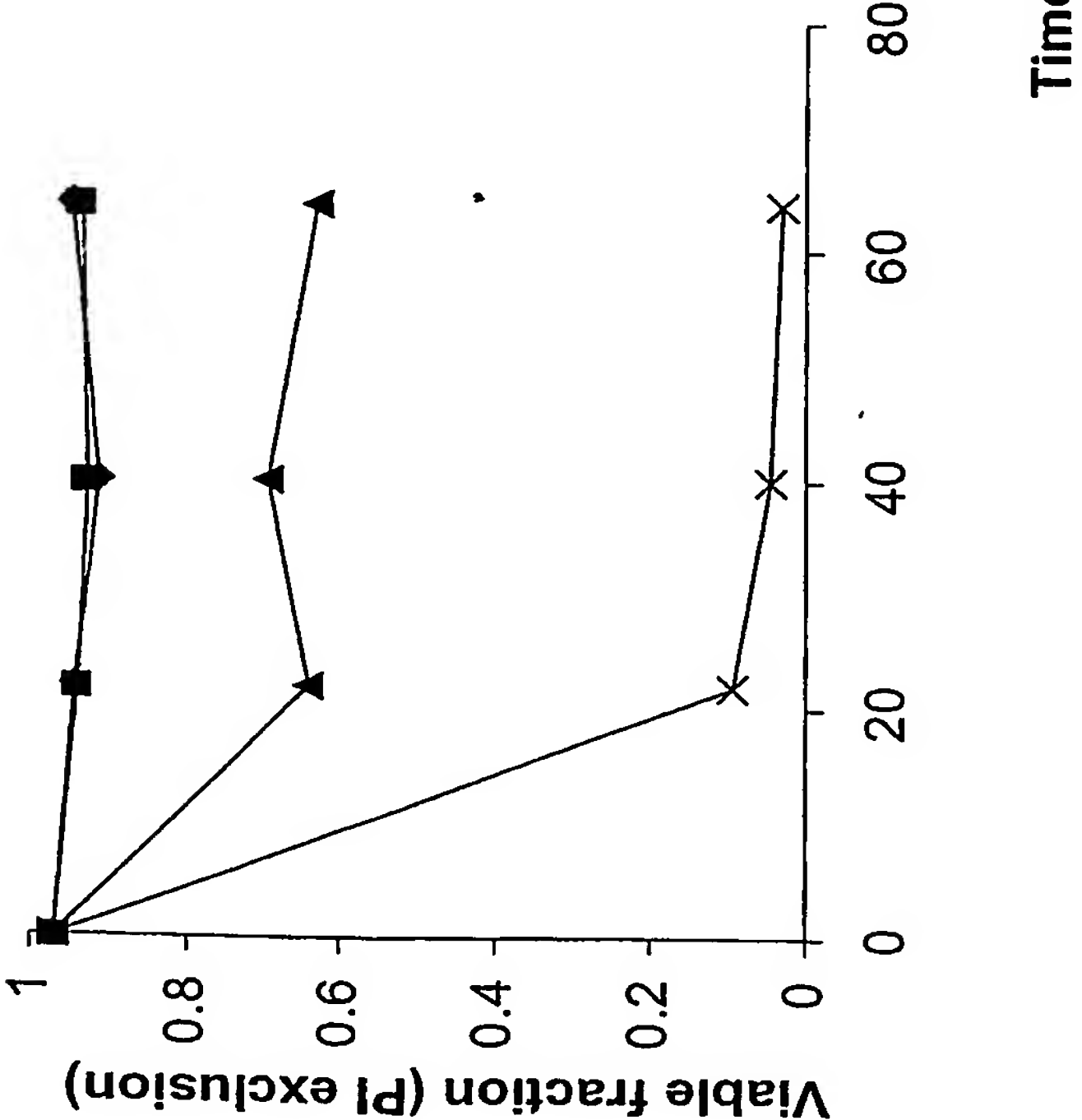
Figure 12B

Proliferating cells are more sensitive to
ACL inhibition-induced apoptosis

Bax^{-/-}Bak^{-/-} minus IL3 for 5 days



Bax^{-/-}Bak^{-/-} plus IL3



—♦— vehicle —▲— 30 μM SB204990
—■— 15 μM SB204990 —×— 60 μM SB204990

Figure 13

ACL inhibition prevents growth factor-induced
cell growth and cell cycle entry

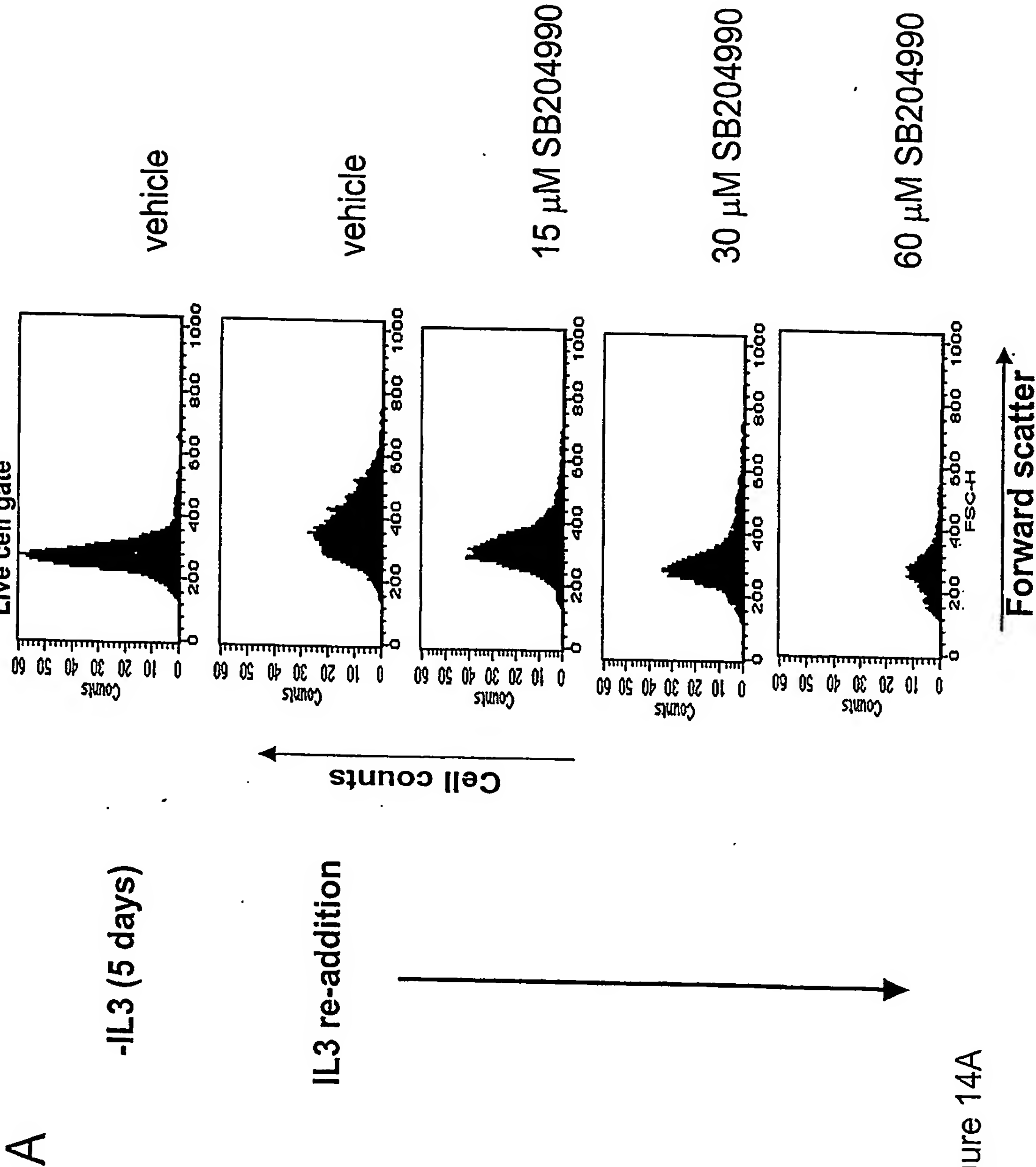


Figure 14A

ACL inhibition prevents growth factor-induced
cell growth and cell cycle entry

B

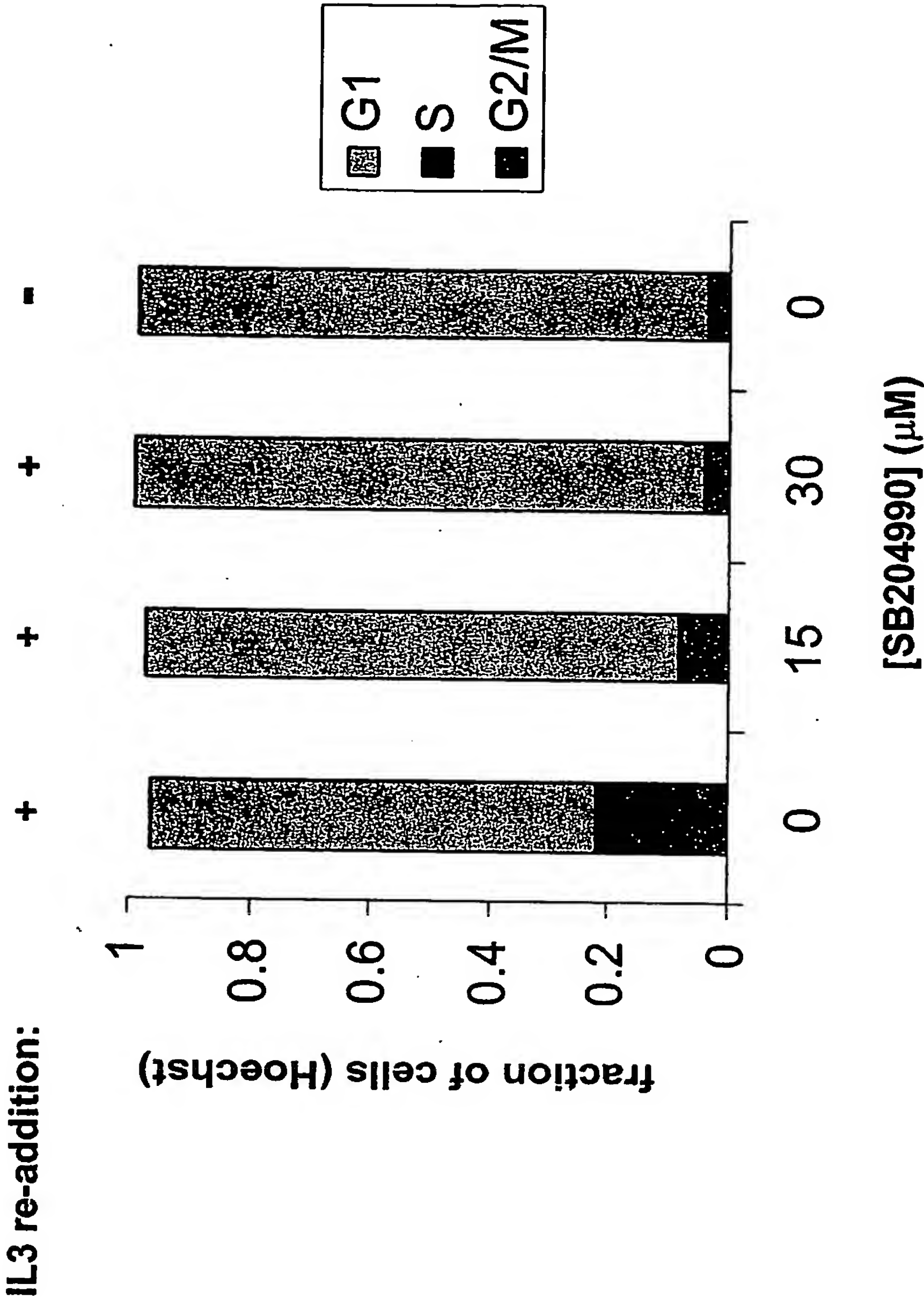


Figure 14B

Mitogenic stimulation makes quiescent cells more sensitive to ACL inhibition-induced death

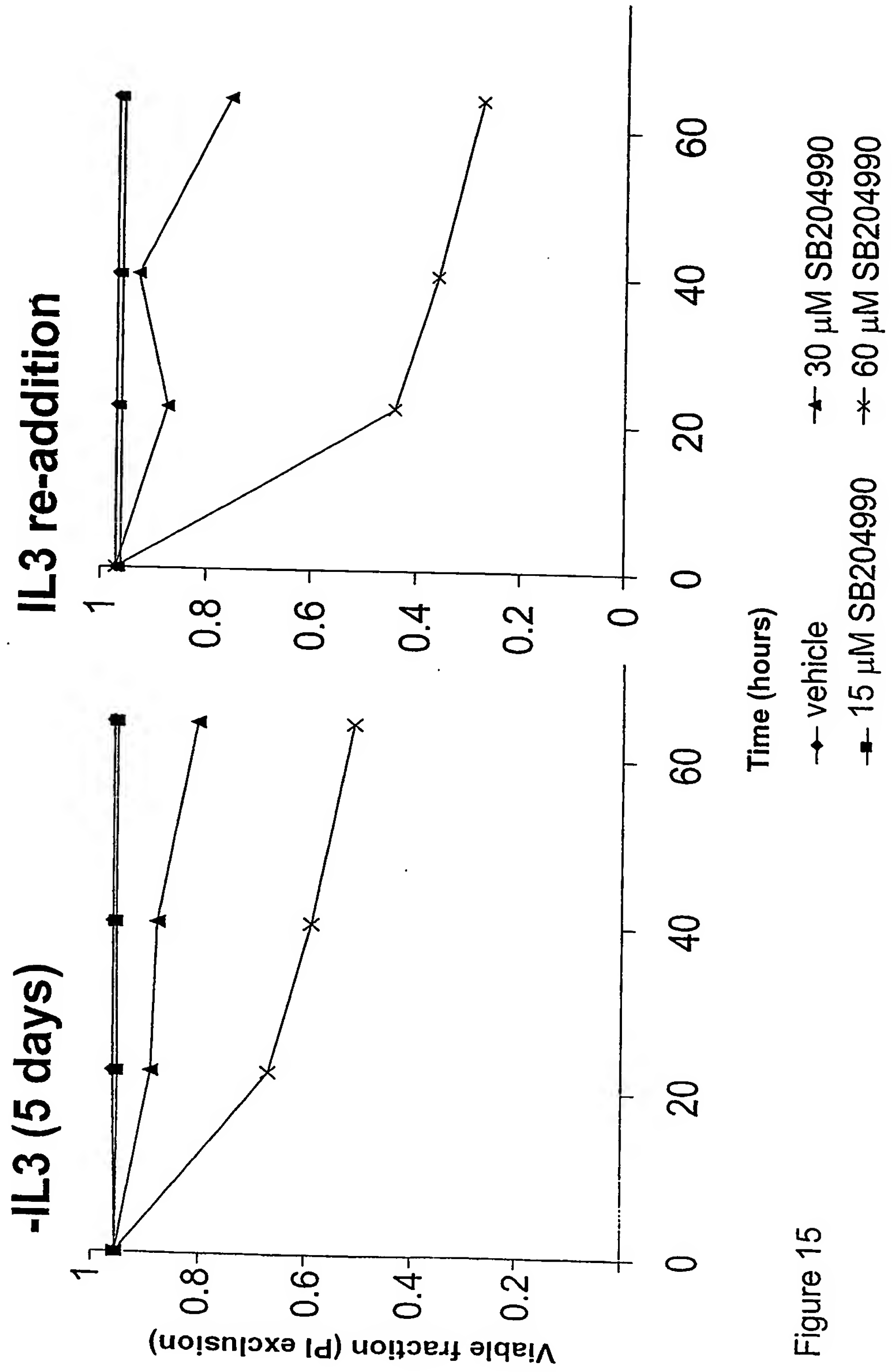


Figure 15

ACL inhibition of cells expressing active Akt decreases their glycolytic rate

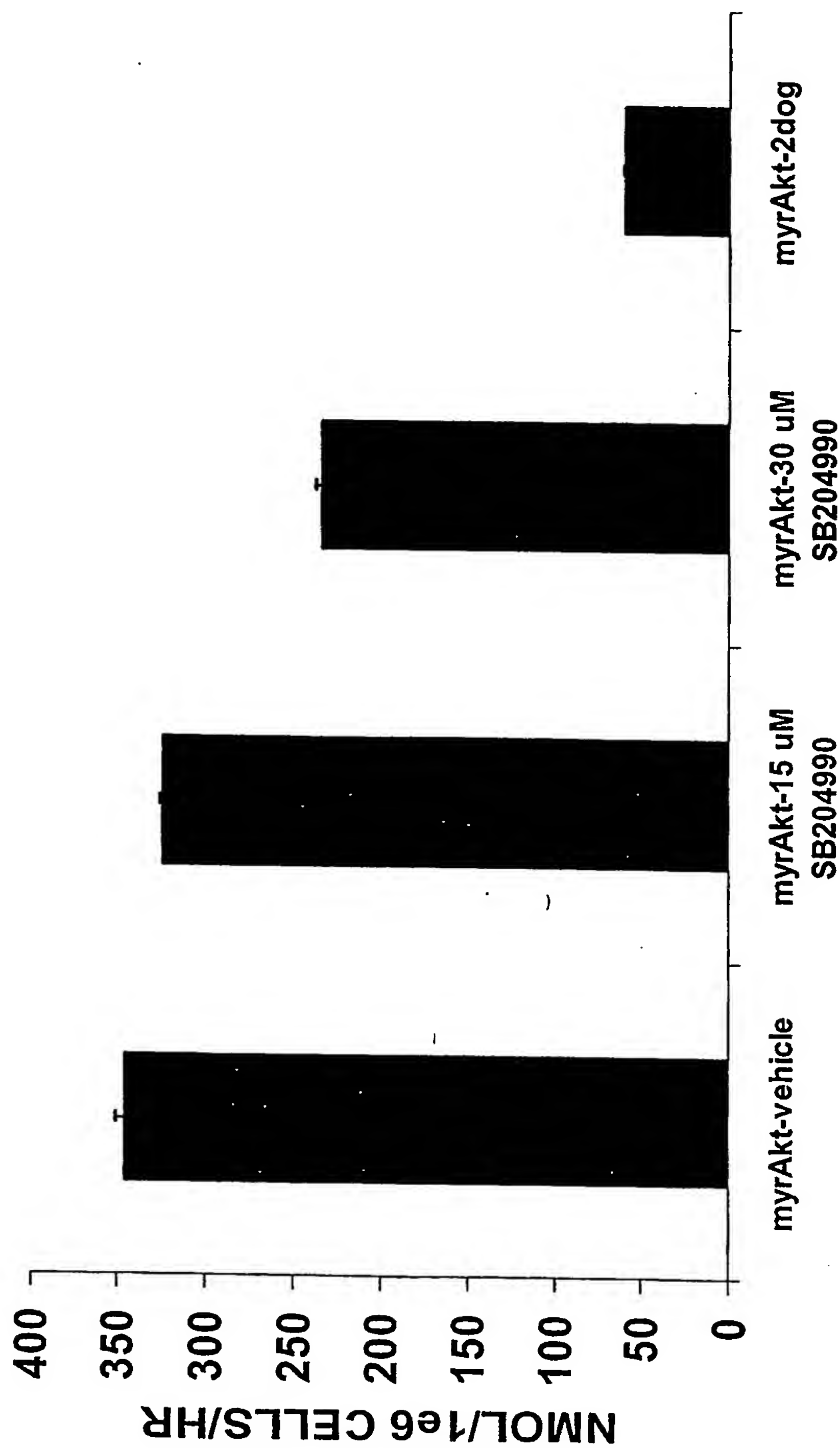
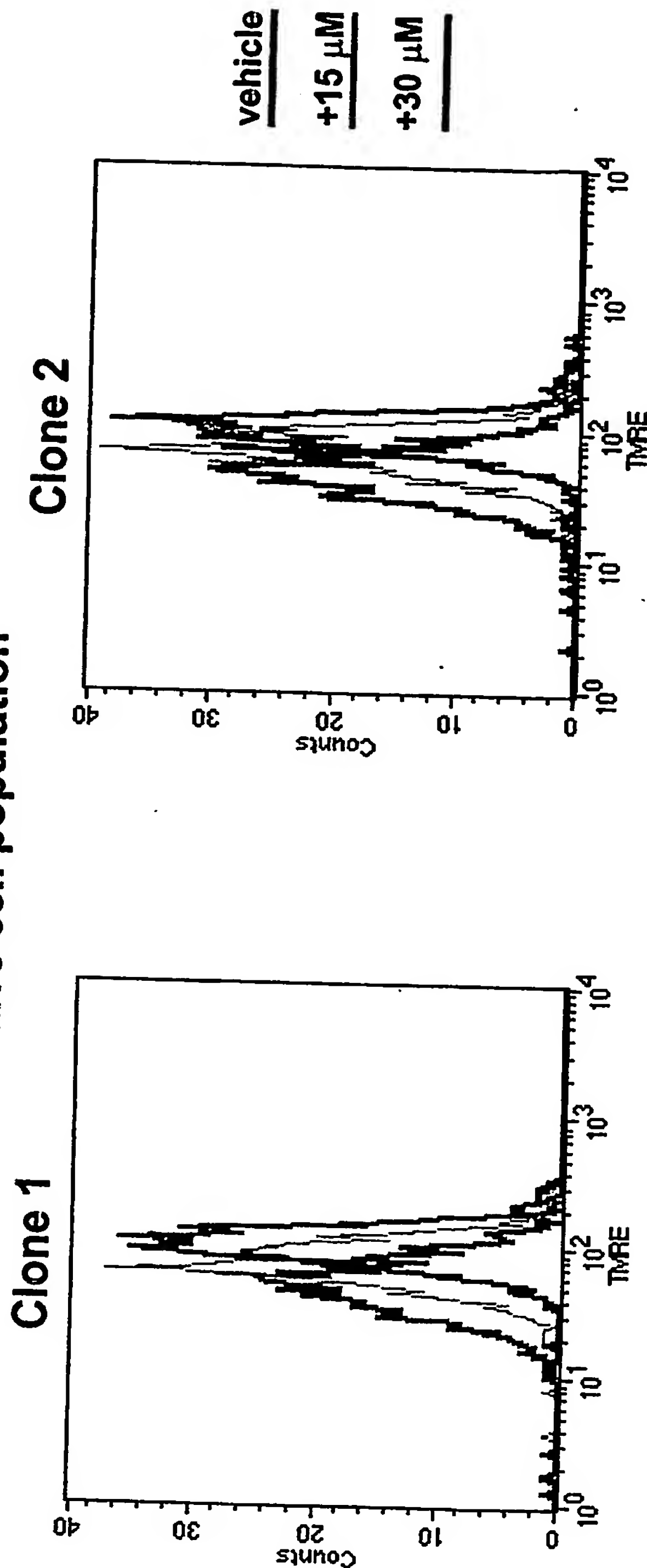


Figure 16

Mitochondrial hyperpolarization upon ACL inhibition is dose-dependent

Live cell population



TMRE Mean Fluorescence Intensity

vehicle
53.66
+15 μ M SB204990
76.41
+30 μ M SB204990
100.41

vehicle
47.88
+15 μ M SB204990
73.12
+30 μ M SB204990
95.23

Figure 17

**ACL inhibition induced mitochondrial hyperpolarization
precedes annexin V positivity**

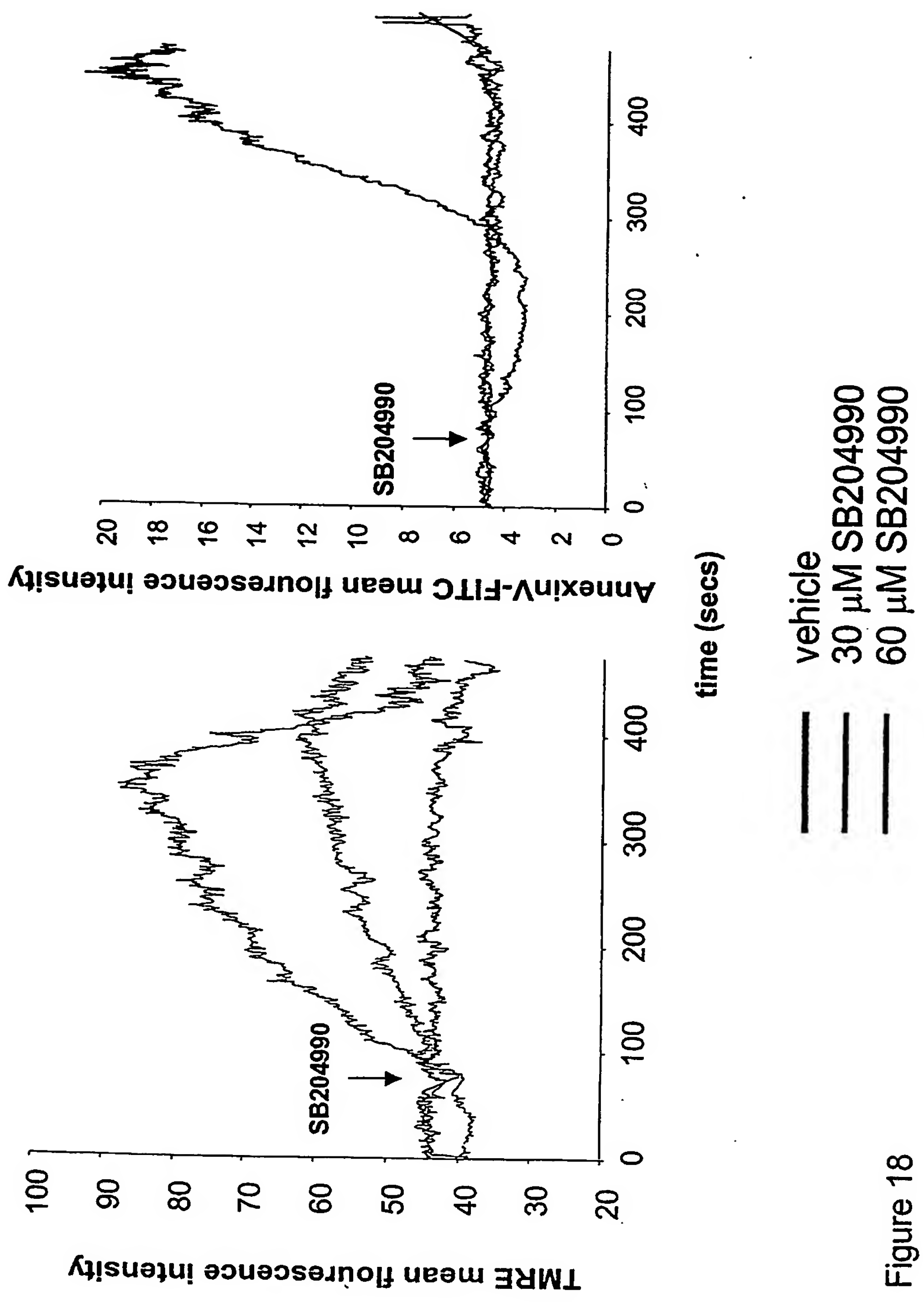


Figure 18